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Review of the Health Effects of Sulfur Oxides

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The pollution in the air is a complex mixture of chemical substances of varying toxicity of which the sulfur oxides are a principal component. Those components which pose the primary hazards to human health have not yet been fully identified, nor have their respective contributions to human disease been fully determined. Efficient and effective control strategies are dependent upon the identification and understanding of these toxic components. Ultimately, the goal of standard-setting should be the development of composite pollution indices rather than control of individual pollutants.

Concentrations of SO_2 in the ambient air twice the current standards are associated with adverse health effects. A considerable body of evidence suggests that there may be discernible human health effects from exposure to concentrations approximating the current standards. There is therefore no basis for relaxation of the present standards for sulfur oxides at this time. Since the scientific basis for this judgment is incomplete, further scientific information will be required either to validate the present standards or to justify alteration of these standards.

Review of Health Effects of Sulfur Oxides

Background and Objectives of the Study

Mr. Roy Ash, Director of the Office of Management and Budget, requested the Department of Health, Education, and Welfare to take the lead in a cooperative study with the Environmental Protection Agency to examine the existing scientific information on the health effects of sulfur oxides in the ambient air. Specifically, Mr. Ash asked:

> "We are particularly interested in an assessment of the adequacy of current information on the ambient levels of sulfur oxides to ascertain the extent to which human health is affected. If a definitive statement cannot be provided on the basis of current information an outline of the types of studies necessary to provide a definitive level should be developed. Assuming that additional studies may be necessary, we would appreciate receiving an estimate of the time required and costs to complete the additional studies."

A report on the following specific areas was requested: (1) the extent of the demonstration of a cause-and-effect relationship between exposure to sulfur oxides and adverse health consequences, including the issue of dose-effect relationships; (2) the degree to which these findings are supported by epidemiologic, clinical,

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and experimental or laboratory studies, including matters of agreement or disagreement among the findings produced by the various study approaches; (3) the variable susceptibility to adverse effects of sulfur oxides among different population groups; (4) a quantification of health effects in relation to various levels of exposure; and (5) the relationship between various levels of sulfur oxide exposure and costs in terms of impaired health, including the costs of care and loss of productivity among those who are or may be adversely affected by exposure to sulfur oxides.

This study has examined the existing scientific information and answered, insofar as is possible, these important questions. It is clear that additional information on the health effects of sulfur oxides is urgently needed. A program of research studies designed to develop such information is therefore included.

Summary of Available Information

The chemical form of sulfur oxides in the ambient air which is associated in epidemiological studies with morbidity and mortality has not yet been clearly identified. The sulfur-containing products which have been implicated include SO_2, sulfuric acid, and inorganic sulfates. SO_2 gas is generated primarily by the process of burning fossil fuels containing sulfur. SO_2 remains in the ambient air for 1–7 days, during which time it can be converted to sulfates and sulfuric acid by sunlight, photochemical oxidants, or by the catalytic effect of certain particulates in the air. These processes are complex and not quantitatively understood. SO_2 in the ambient air therefore provides a reservoir from which the more toxic sulfates and sulfuric acid derive. On a nationwide basis, the average ambient air concentrations of SO_2 have been decreasing in the last few years because fossil fuels with a lower sulfur content have been used. The concentration of suspended sulfates in the air has not correspondingly decreased since 1963 and appears to be highest over the northeast section of the nation.

Studies on laboratory animals and human volunteers have shown that inhalation of SO_2 alone does not affect lung function at concentrations 10 to 100 times that commonly found in ambient air. Mixtures of SO_2 and particles are often more toxic than SO_2 alone, the toxicity depending on the SO_2 concentration, the nature and size of the particles, and the ambient relative humidity. Particles can absorb SO_2 and facilitate its reactions. Airborne particulate metals (vanadium, manganese, iron, etc.) catalyze the conversion of SO_2 to sulfuric acid and sulfates. Sulfuric acid and acid sulfates have proved to be particularly toxic in animal experiments.

Studies in animals are helpful in determining mechanisms of action in the body, but are not suitable for establishing safe levels for human exposure. The number of animals tested has been small relative to the human population at risk daily. The animals are selected to be healthy, vigorous, and young whereas the humans most susceptible to pollutant effects are the diseased, very young, or aged.

For estimates of safe levels, we must turn to epidemiologic studies which relate environmental factors including pollution to states of health or disease.

Health effects may range from discomfort through physiological deviations from the norm, prevalence of symptoms, appearance of illness, lost working time, and premature retirement to complete incapacity and death. In practice, it is better to consider these indices in the reverse order, starting with death, serious illness, and significant disability, about which there can be little argument, and to proceed thence to physiological deviations and minor disorders, the significance of which may be open to question. Disease and death seldom, if ever, result from pollution alone. They are the outcome of many factors, both individual and environmental, acting together. Any epidemiological study of the effects of air pollution must allow adequately for these other factors. Indeed, the quality of such studies often depends on the success with which such allowance has been achieved. At the other end of the range of health effects, the implication of minor symptoms and small deviations from some physiological or biochemical norm between persons living in polluted and nonpolluted neighborhoods may be imperfectly known. Until it can be shown that such effects predispose to disease, disability, or reduced expectation of life, the weight that should be given to them in setting standards

will remain a matter for personal judgment.

Acute episodes of high pollution have clearly resulted in mortality and morbidity. Often the effects of high pollutant concentrations in these episodes have been combined with other environmental features such as low temperatures or epidemic diseases (influenza) which may in themselves have serious or fatal consequences. This has sometimes made it difficult to determine to what extent pollution and temperature extremes are responsible for the effects. Nevertheless, there is now no longer any doubt that high levels of pollution sustained for periods of days can kill. Those aged 45 and over with chronic diseases, particularly of the lungs or heart, seem to be predominantly affected. In addition to these acute episodes, pollutants can attain daily levels which have been shown to have serious consequences to city dwellers. For many years in London, daily deaths and illnesses were clearly related to daily levels of smoke and SO_2. Comparable observations have been made in New York City, Philadelphia, and Chicago. In the New York–New Jersey Metropolitan area, an analysis of daily mortality for the years 1962–66 showed that deaths were 1.5% below expectation at the lowest SO_2 concentrations and 2% above expectation at concentrations of 500 $\mu g/m^3$ and above. A similar though weaker relationship was found in Philadelphia but not in Chicago. This work urgently needs to be pursued, since it calls into question the concept of a no-effect level on which present air quality standards are based.

The implication of daily levels of SO_2 and particulates has been studied in particularly vulnerable groups, such as patients with chronic bronchitis and emphysema. Deterioration in their respiratory well being has resulted from a daily concentration of SO_2 of about 500 $\mu g/m^3$ which is not much above the 24-hr primary standard. A few studies have even suggested that deterioration in particularly vulnerable groups may occur with daily concentrations which are below this standard. Confirmation of this is urgently needed.

There is a large and increasing body of evidence that significant health effects are produced by long-term exposures to air pollutants. Acute respiratory infections in children, chronic respiratory diseases in adults, and decreased levels of ventilatory lung function in both children and adults have been found to be related to concentrations of SO_2 and particulates, after apparently sufficient allowance has been made for such confounding variable as smoking and socioeconomic circumstances.

It is not possible to state a concentration below which such health effects will not occur. In many studies the proportion of persons affected increases from the lowest to highest categories of pollution. Had even lower categories of pollution been used in the analyses, even lower critical levels might have been suggested.

Thus, as in the case of daily mortality, the concept of no-effect level may be a chimera. A reasonable conclusion from these studies would however be that health effects have been found when annual levels of particulates or SO_2 exceed 100 $\mu g/m^3$. The primary SO_2 annual level thus appears to be low enough but not excessively low.

The need for more information about the lowest levels of pollution which might produce significant effects was recognized by the Environmental Protection Agency through the Community Health and Environmental Surveillance System (CHESS) studies. The CHESS studies were intended to provide this information. These studies were also intended to monitor any changes in health which might occur as a result of any change in pollution concentrations. It is probably safe to say that, in attempting to provide a large amount of information as quickly as possible, the CHESS studies have as yet been less effective than they might have been had a more deliberate approach been adopted. Any defects in design, methods, and execution of these studies, however, can be remedied for the future. The importance of the monitoring aspects of this program can hardly be exaggerated. It is essential that the technique of monitoring be impeccable. Present assessment of the CHESS studies is that they do not in themselves justify and change in the standards. The CHESS studies also provide some support for the viewpoint that acid sulfates and sulfuric acid may be more important pollutants than SO_2 in terms of their health consequences. Further information on this is urgent. In particular, better evidence is needed to suggest an appro-

priate standard for sulfates. There is some evidence that local controls of SO_2 (by higher stacks, etc.) is leading to a wider dissemination of particulate sulfates. All this is resulting in a rather uniform level of sulfates in the northeast United States. Should sulfate concentrations rise uniformly over a wide area, it might be impossible to find any appropriate low sulfate control areas with which any putative health effects should be compared.

Catalytic converters which are to be installed on automobiles to control pollution may become a new source of increased sulfates and sulfuric mist in the breathing zone of urban areas. This may pose potentially severe problems in areas saturated with automobile use. The exhaust from cars with catalytic converters contributes only a small portion of the atmospheric sulfate, but this may be disproportionately significant because it occurs in the breathing zone of a large portion of the urban population.

Summary of Key Problems

The first problem concerns the identification and isolation of the ultimately toxic pollutant(s). SO_2 has often been used as an index of pollution and is sometimes considered a main pollutant. SO_2 alone is of relatively low toxicity, but in the presence of other pollutants, such as total suspended particulates (TSP) or ozone, or after conversion to particulate sulfate or sulfuric acid, it can become a major contributor to adverse health effects. Yet SO_2 and TSP (of which sulfates are a variable fraction) are the measured pollutants to which controls are directed. Operationally, to prevent the health consequences of SO_2-related pollution, we must know more of the interrelationships between these sulfur oxides, the effects of particle size, the importance of particulate composition, the synergistic toxicity between SO_2, particles, and humidity, and the adverse health effects of suspended sulfates and sulfuric acid mist.

Further studies are crucial for sound policy. It is possible that a policy decision to reduce SO_2 alone without control of particulates could well lower our SO_2 pollution index but yield no benefits for health. Likewise, an attempt to clean the air of particulate matter without controlling SO_2 might preferentially clean up the more manageable large particles and effect a marked improvement in the TSP index while leaving the smaller, more toxic respirable-sized particles for man to breathe. We must aggressively seek a broader and firmer scientific foundation on which to base present and future policies. These policies will affect billion dollar decisions and involve the health and well being of millions of Americans. In the area of air pollution policy, inertia and inactivity without research support is in itself a multibillion dollar decision.

The second problem concerns the importance of epidemiologic data in arriving at a primary ambient standard. While we may review the present air criteria levels many times and underscore the incomplete data base, we must also realize that epidemiologic evidence will be central to any future reevaluation of the present standards. These studies require years to complete land demand continued support over long periods of time.

In this regard, the continuing results of the CHESS studies will be of great assistance in improving our estimate of a no-effect level for SO_2. The community of epidemiologists and scientists outside EPA is not adequately familiar with the details of these very extensive studies to endorse or challenge the reported results. In the normal course of scientific investigation, review, and publication, such understanding and acceptance or rejection would occur. This process however would take years, and the answers are needed now.

It would be important for EPA to assemble a group of academic and government epidemiologists to provide in-depth review of the mass of data from this ongoing program and offer continuing advice. Furthermore, consideration should be given to having complementary studies performed by extramural organizations.

In the near future, pollution levels will fall in some areas and may rise in other areas if high sulfur fuel must again be burned. Our understanding of the effects of pollution on health could be significantly advanced if epidemiologists with foresight and funding could set up studies now of the temporal consequences on the health of the exposed populations of these unplanned experiments.

Both of these approaches to setting air quality

criteria involve the input of well trained chronic disease epidemiologists, a commodity which is in short supply within the American medical community.

The third problem concerns the generally inadequate data base upon which these standards rest. These standards will affect the lives and health of millions of people and influence the expenditure of billions of dollars. The bulk of the laboratory animal studies which have delineated the synergistic toxicity of SO_2 and certain particles has been performed in a single laboratory over the last two decades and cost in the aggregate, approximately $600,000. It is fortunate that this single investigator did not choose another research topic 20 years ago.

When the research data base for standard setting is inadequate and the margins of error are large, prudence dictates a conservative approach. Standards will be set at more stringent levels to insure that the public health is protected. More information can decrease the margins of error and result in more realistic perhaps less stringent standards.

The range of uncertainty in the study of the adverse health effects of SO_2 and particulates has been quantified in the CHESS reports as the "worst" and "least" case examples. The potential risk of a wrong decision includes: (1) accepting the lowest levels (worst case) to be significant to health when this is not true and consequently wrongly promoting expensive pollution controls, or (2) accepting the highest levels (least case) to be significant when this is not true and consequently wrongly allowing many people to suffer the ill effects of pollution toxicity. In our uncertainty rests a multibillion dollar decision which could have potentially disastrous consequences for future Americans. Our need to make this decision on a more secure scientific basis is imperative.

Answers to Specific Questions Posed by the Office of Management and Budget

(1) Cause-and-Effect Relationship between Exposure to Sulfur Oxides and Adverse Health Consequences: Cause-and-effect relationships probably exist at ambient air concentrations of sulfur oxides somewhat above the current standards in the United States today, perhaps at twice the current standards. Some studies suggest these relationships also exist at concentrations in the range of the primary ambient air standards for SO_2 and TSP. Tentative exposure–effect relationships are available, but must be treated as suggestive, not definitive.

(2) Agreement with Epidemiologic, Clinical, and Experimental or Laboratory Studies: The clinical, laboratory, and experimental studies at relatively high concentrations of sulfur oxides in the ambient air are consistent with the current epidemiologic data. Information is not available to provide the desired level of confidence at concentrations approximating the current standards. This can be corrected by the fuller development of the needed information.

(3) Susceptibility to Adverse Effects of Sulfur Oxides of Different Population Groups: The population groups of particular concern are young children, the elderly, and any persons with pre-existing diseases of the heart and lungs.

(4) Health Effects at Various Exposure Levels: The purpose of many epidemiologic studies is to define an exposure–response relationship. The best available tentative exposure–response curve is presented in Figure 1. An imaginative attempt to group the

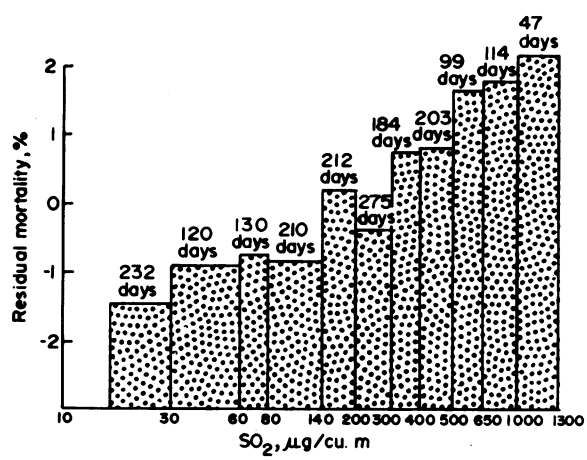

FIGURE 1. Dose—response curve for SO_2. Means of residual mortality by SO_2 class in New York-New Jersey metropolitan area, 1962–1966 (1826 total days). Data of Buechley *(1)*.

graded health consequences of exposure to SO_2 against a composite index is illustrated in Figures 2 and 3.

(5) Relationship Between Sulfur Oxides Exposure and Costs in Terms of Impaired Health: We are not convinced that there are currently available reliable estimates of the number of people affected by SO_2. A cost estimate is given in Table 1, but we are not convinced of the validity of the methods used to derive these figures.

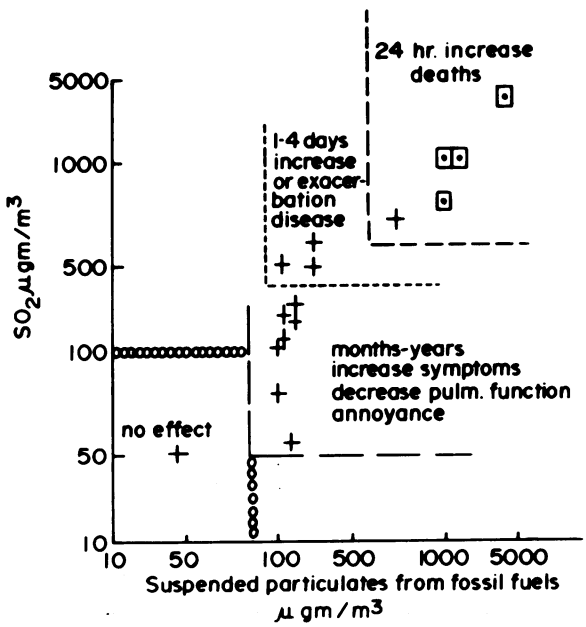

FIGURE 2. Dose—response curve for sulfur dioxide. Data of Dr. Benjamin Ferris (personal communication).

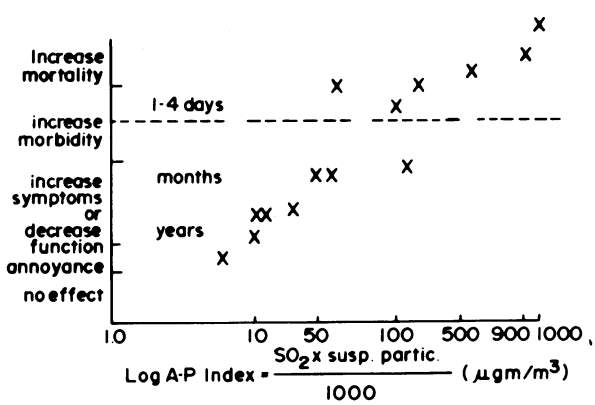

FIGURE 3. Dose—response curve for total suspended particulates. Data of Dr. Benjamin Ferris (personal communication).

Table 1. Estimates of the cost of the health consequences of air pollution.

Study	Cost, $\$x10^{-9}$	Considerations
Waddell *(2)*	0.9–3.2	SO_x effects on human health.
	1.6–7.6	Particulates + SO_x combined effects on human health.
	7.1–20.1	All measurable adverse environmental effects
Lave *(3)*	7.0	Total health benefit that would accrue in 1978 based on 1970 dollars and 1969 data

Research Proposals Designed to Provide Needed Information on Health Effects of the Sulfur Oxides

Research efforts designed to develop needed information on the health effects of the sulfur oxides are outlined in Table 2.

Laboratory Research on and Monitoring for the Multiple Factors in Sulfur Oxide Toxicity: It is important to delineate which specific compounds in the mixture of present pollutants are ultimately damaging to pulmonary structure and function. It will be impossible to develop well designed and effective control programs until more information is available on (1) the toxicity of SO_2, various sulfates, and sulfuric acid mist and on (2) the conditions necessary for the interconversions of these sulfur oxides.

The proposed program (Table 2) includes monitoring, atmospheric chemistry research, and biomedical research.

Epidemiologic Research: Ultimately the development of proper cost effective ambient air standards depends on epidemiologic evidence. A number of steps should be taken to provide for this necessary epidemiological evidence. These are summarized in Table 3.

As circumstances develop, SO_2 levels may be projected to fall in some areas and to rise in others if return to high sulfur fuel becomes inevitable. Advantage should be taken of this situation by initiating a prospective study designed to document the health effects of

Table 2. Laboratory research on and monitoring of multiple factors in sulfur oxide toxicity.

Program	Estimated cost, $/yr	Duration, yr	Estimated time to achieve significant results, yr
A. Intensify study of qualitative and quantitative aspects of the interconversions between SO_2, suspended sulfates, and sulfuric acid mists; rates and routes of conversion and residence times of intermediates and end products are important	700,000	4	2
B. Develop and validate methods for monitoring suspended sulfates and sulfuric acid mist	400,000	2	2
C. Develop a national monitoring system for suspended sulfates and sulfuric acid mist	600,000–2,000,000		3
D. Maintain the present National Air Sampling Network and keep surveillance and quality control tied into the EPA Office of Research and Development	None		1
E. Continue the development of atmospheric air pollution	600,000	5	2
F. Investigate the pulmonary responses and toxicity in laboratory animals and in human volunteers of the various sulfur oxides under various conditions of humidity and specific particulates of differing size	2,000,000	4	3

Table 3. Program of epidemiologic research.

Program	Estimated cost, $/yr	Duration, yr	Estimated time to achieve significant results, yr
A. Study to document the health effects of variations in concentration of ambient sulfur dioxides	1,000,000 Lesser amounts	5 10	5
B. Studies by academic institutions	1,000,000	6	4
C. Strengthening of CHESS study by outside input and review	150,000 100,000	1 thereafter	1
D. Study of daily mortality rate in New York City			
1. Extend this study to present	300,000	1	1
2. Provide resources for the National Center for Health Statistics to maintain daily mortality data for future studies	40,000		1–2
3. Continue New York study on ongoing basis	150,000		2
4. Extend similar studies to three other cities	500,000		2
E. Design and fund a manpower training program to recruit more chronic disease epidemiologists	500,000	10	4–5

these changes. This study is of such a critical nature that a more detailed description is given in the following section.

In order to replicate certain of the very important studies encompassed in the CHESS program it would be useful to invite academic institutions to initiate studies in certain critical areas.

It is necessary to strengthen the CHESS study by providing the opportunity for extensive outside input and review. With such review the CHESS results will be increasingly important. (The estimates in Table 3 do not include funding for the CHESS program which should be continued.)

The study of the daily mortality rate in the New York City Metropolitan area as related to daily SO_2 concentrations has provided important information. This study was terminated in part because the National Center for Health Statistics stopped coding mortality on a daily basis. Extension of the study to the present (if SO_2 levels continue to fall) and to the future (if SO_2 levels rise) would be very important.

The continuing critical shortage of epidemiologists is a major impediment to further definition of the health effects of air pollution.

Every critical review of the relationship of environmental factors to health calls attention to the inadequacy of the quantity or quality of epidemiologic studies. One of the reasons for this is the serious shortage of qualified environmental epidemiologists. Most epidemiologists are oriented to the study of the infectious diseases; substantially different orientation and different skills are necessary for effective study of chronic noninfectious diseases. Sophisticated methods are required, which take into account not only the biologic characteristics of people (age, sex, race, genetic defects, etc.) but also the great variety of external or environmental factors which influence health and disease (social class, season, occupation, personal habits such as smoking and drinking, diet, place of residence, etc.).

Whereas some medical specialists have been trained in excess in recent years, this is not the case with this kind of epidemiologist. In fact, the opposite is true — among all medical specialities, this one is probably in shortest supply compared to need.

Training facilities for this type of epidemiologist are also very limited. There are a few training centers in schools of public health and medical schools but no center in the Federal government, in contrast to the outstanding facility operated at the Center for Disease Control for many years, for training of infectious disease epidemiologists.

Opportunities exist for increasing the number of epidemiologists by combining the resources of academic institutions and the Federal government. If funds were available, existing university centers could substantially increase trainees without much increase in faculty. The Federal government has resources for field training; for example, in several institutes of NIH, EPA, NIOSH, and the NCHS. Academic institutions and Federal agencies should work together to develop an integrated program. Opportunities for training should be open to college graduates and should not be limited to physicians, dentists, and veterinary physicians.

Research Proposal to Maximize Information on Human Health Effects from Projected Alterations of Concentrations of Ambient Sulfur Oxides: Review of the available information concerning the health effects of sulfur oxide air pollutants reveals significant deficiencies in the extent of knowledge available to base judgements concerning appropriate control strategies. In view of the current shortage of low sulfur fuels, a significant deterioration in regional air quality is expected to develop this winter and to be repeated for a number of years subsequently. Dr. Frank Speizer of Harvard University has submitted a preliminary outline of studies aimed at determining the health effects of increased ambient levels of sulfur oxides brought about by the reintroduction of high sulfur fossil fuels. The approach consists of epidemiological evaluation of the health of population groups who will be inevitably subjected to elevated ambient levels of sulfur oxides due to use of high sulfur fuel. Its goal is to provide information relevant to establishing appropriate standards and control strategies for sulfur oxides.

The studies are based on a number of assumptions which include the ability to forecast which parts of a definable geographic area will have the

worst air quality, the ability to obtain long-term commitments for large-scale cooperative studies from national, state, and local institutions, and the availability of sufficient numbers of trained personnel to perform the studies.

Studies of acute effects would focus on respiratory disease in cohorts of school children, normal adults, and high risk groups followed for up to five years. Evaluation of school children is envisioned to involve approximately 1000 subjects, age 9–12, divided into three groups depending upon exposure levels. Respiratory illnesses, school absences, and pulmonary function would be monitored. New groups of 9-year-olds would be added yearly in order to provide data on the cohort effect of changing levels of pollutants. The estimated cost would be $75,000–$100,000/yr per 1000 children.

Studies of normal adults would consist of identifying cohorts living in areas with the same pollution or cohorts receiving similar occupational exposures to dust who would be evaluated with repeated biennial assessment of respiratory symptoms, work days lost, hospitalization, etc., particularly during high exposure periods. Control groups would be from relatively unexposed areas. Cost per subject is envisioned to be in the same range as the study of children but more subjects will be needed due to the confounding effects of smoking.

The special risk groups to be studied would consist of "normal" (i.e., least detectable change) subjects who have been identified to have relatively decreased pulmonary function in a screening program, patients previously hospitalized for respiratory failure, and asthmatics of all ages. No cost estimates are given.

to evaluate whether these levels of sulfur oxides have real chronic effects would require follow-up of these cohorts for at least 10–15 yr beyond the initial acute studies described above. A formal registry system of this type appears feasible in school children and also may be practicable in other population groups.

Background Review: Atmospheric Chemistry

Sulfur oxides in the atmosphere can most conveniently be considered as occurring in three forms: sulfur dioxide (SO_2), sulfuric acid (H_2SO_4), and inorganic sulfates.

Sulfur dioxide is the anhydrous form of the weak acid, sulfurous acid (H_2SO_3). The salts of this acid are known as sulfites and bisulfites. These have not usually been searched for in the atmosphere as it is believed that essentially all sulfur dioxide is eventually oxidized to sulfates, either in air or following absorption by plants or adsorption on surfaces.

Sulfuric acid is the hydrated form of sulfur trioxide (SO_3), which is derived from the oxidation of sulfur dioxide. As sulfur trioxide is intensely hygroscopic, it is almost immediately converted into sulfuric acid in the atmosphere.

Inorganic sulfates are presumably derived from either the reaction of sulfuric acid with cations or by the oxidation of sulfites. There is little information available concerning the possible formation of organic sulfates in the atmosphere.

The major source of urban sulfur oxides is the combustion of fossil fuels in stationary sources. Approximately 98% of the sulfur released to the air is in the form of sulfur dioxide and most, if not all, of the remainder is sulfuric acid. Inorganic sulfates may also be discharged preformed in certain industrial effluents. It must be emphasized that while almost all of the sulfur dioxide produced by combustion of fossil fuel is eventually converted into sulfate, not all atmospheric sulfate is derived from this source. Natural sources of sulfur dioxide and hydrogen sulfide (H_2S) can be oxidized to sulfate. Aerosols of sea water are a direct source of atmospheric sulfate *(4, 5)*. While it has been estimated *(5)* that only one-third of the sulfur in the entire global atmosphere is derived from pollutant sources, this observation is not pertinent to local respirable ground levels of sulfur oxides which in urban areas are almost entirely derived from fossil fuel combustion.

The formation of sulfates from sulfur dioxide in the atmosphere may best be viewed as two separate, although perhaps related, chemical processes. The first is the oxidation of sulfur dioxide to sulfuric acid and the second is the reaction of sulfuric acid with cations to form sulfates. Sulfur dioxide in pure air is very slowly oxidized by sunlight to sulfuric acid with a rate of about 0.1%/hr *(6)*. While there is inadequate information to characterize fully the chemical processes by which sulfur dioxide is oxidized in polluted urban air, the conversion is much more rapid than in pure air. This is due to the pres-

ence of other air contaminants which in general greatly facilitate the oxidation of sulfur dioxide. Two processes appear to be involved: oxidation by components derived from photochemical processes *(7–12, 34)* and catalytic oxidation predominantly by certain types of particulate aerosols *(13–21)*. The photochemical reaction is associated with the action of sunlight on oxides of nitrogen and hydrocarbons derived primarily from mobile sources. The ensuing reactions result in the production of agents capable of oxidizing sulfur dioxide to sulfuric acid. As an illustration of the complexity of this process, the presence of sulfur dioxide in the photochemical mixture enhances aerosol formation thereby tending to decrease sunlight which in turn decreases the rate of photochemical reactions. Estimated rates for the oxidation of sulfur dioxide due to the photochemical process range as high as 18%/hr/(S. K. Friedlander, personal communication, Sept. 1973). Rate data are summarized in Table 4.

Catalytic oxidation of sulfur dioxide occurs in the absence of sunlight in aerosols on which sulfur dioxide has been adsorbed. Major research interest has focused on the catalytic role of metallic compounds in the aerosols including manganese, iron, vanadium, aluminum, lead, and copper. The total reaction is a highly complex process with many interrelated variables which are poorly characterized *(34)*. These include adsorption rate of sulfur dioxide, particle or droplet size, chemical composition, rate of diffusion of reactants within the aerosol and relative humidity. Relative humidity is a major determinant, as the reaction occurs in water droplets containing the metallic particulates and absorbed sulfur dioxide. Furthermore, as an acid pH decreases the rate of sulfur dioxide oxidation, the formation of sulfuric acid in the aerosol would tend to be self-limiting unless the acidity is diluted by additional water vapor. In this respect, alkaline metal compounds (e.g., iron oxide) and ammonia also enhance the reaction rate by decreasing droplet acidity through their buffering capacity. Extrapolated levels for the rate of oxidation of sulfur dioxide by catalytic processes in urban air range upwards of 2%/hr.

Weather has a great effect on these atmospheric chemical processes. Inversion levels will dictate the concentration of sulfur oxides and other contaminants thereby influencing the rate at which they react. Increased humidity accelerates catalytic oxidation of sulfur dioxide, while cloud cover might be expected to lower the rate of the photochemical process, and rain will wash out sulfur oxides from the atmosphere. Temperature affects reaction rates and the solubility of gases. Wind influences the rate, direction, and distance of dispersal.

The average residence time of sulfate in the atmosphere is probably measured in days. A large urban source of sulfur dioxide will therefore result in increased atmospheric sulfates being present many miles downwind. In regions where there are multiple urban sources of sulfur oxides, such as the northeastern United States, there has been a general buildup of ground level sulfates stretching many hundreds of miles *(29)*. This includes rural areas which have appreciable suspended particulate sulfate concentrations despite relatively negligible sulfur dioxide levels. In view of the possible toxicity of suspended sulfates, it should be noted that emission control measures designed to disperse sulfur dioxide from point sources, e.g., tall stacks, will not have a major effect on area-wide suspended sulfate levels despite producing a decrease in local ambient sulfur dioxide concentrations. Also of note is the finding that the ratio of sulfur dioxide to suspended sulfate concentrations in eastern cities differs from that in western cities *(30)*. Data from the last decade reveals the sulfur dioxide/sulfate ratio in eastern urban areas to be 4.9 (SO_2, 66 $\mu g/m^3$; SO_4, 13.5 $\mu g/m^3$) and in western urban areas to be 3.4 (SO_2 22 $\mu g/m^3$; SO_4, 6.4 $\mu g/m^3$).

The analytical techniques for the measurement of ambient concentrations of sulfur dioxide, suspended sulfates, and sulfuric acid are not comparable in terms of reliability or accuracy *(30, 31)*. Much information is available concerning ambient sulfur dioxide levels and the assay system is relatively well standardized and believed to be reasonably accurate. Less information about ambient suspended sulfate levels is available, and the assay systems in use have a number of difficulties. Most notable is the possibility that a portion of the sulfates detected on particle traps result from the reaction of sulfur dioxide with the trapping material and do not

Table 4. Estimated sulfur dioxide oxidation rates in the lower atmosphere: tabulation of selected studies

Experimental conditions	Presumed atmospheric conditions	Extrapolated SO_2 consumption rate	Reference
Sunlight; High SO_2 concentrations; no other impurities present	SO_2; sunlight; clean air	0.5%/hr	Hall, *(22)*, cited by Urone and Schroeder *(23)*
Sunlamp in smog chamber; high SO_2 concentrations in pure air	SO_2; sunlight; clean air (reaction unaffected by humidity)	0.1–0.2%/hr	Gerhard and Johnstone *(6)*
Sunlight; 200–2000 $\mu g/m^3$ SO_2; trace impurities	Assuming 300 $\mu g/m^3$ SO_2; bright sunlight for 10 hr would produce 30 $\mu g/m^3$ of sulfate	0.65%/hr (high rate may be due to trace impurities)	Cox and Penkett *(24)*
Smog chamber; light; SO_2, NO_x, olefins	SO_2, 260 $\mu g/m^3$; ozone, 100 $\mu g/m^3$ olefin, 33 $\mu g/m^3$, bright sunlight	3%/hr for pentene; 0.4%/hr for propene	Cox and Penkett *(8)*
Photochemical reactants SO_2 in ppm concentrations	Sunlight; SO_2, 260 $\mu g/m^3$; ozone, 200 $\mu g/m^3$; olefin, 33 $\mu g/m^3$; 40% RH	3%/hr	Cox and Penkett *(9)*
UV-irradiated gas mixtures; NO_x, hydrocarbons, SO_2; high levels	Noon sun	1–3%/hr	Urone et al. *(12)*
Catalyst droplet exposed to high concentrations of SO_2 in humid air	Natural fog containing 1 μ crystals of $MnSO_4$ in droplets; 2600 $\mu g/m^3$ SO_2	1%/min	Johnstone and Coughanowr *(16)*
Metallic aerosol particles on Teflon beads in flow reactor; SO_2; water vapor	Natural fog (0.2 g H_2O/m^3) in industrial area; SO_2, 260 $\mu g/m^3$; $MnSO_4$, 50 $\mu g/m^3$	2%/hr	Cheng et al. *(13)*
Artificial fog in smog chamber; very high levels; SO_2 and metal sulfates	(Levels in smog chamber) 0.6 mg/m^3 SO_2; 2 mg/m^4 Mn SO_4,	0.01%/min at 77% RH 2.1%/min at 95% RH	Johnstone and Moll *(17)*
NH_4SO_4 formation in water droplets exposed to NH_3 and SO_2	100 $\mu g/m^3$ SO_2; 10 $\mu g/m^3$ NH_3; cloud droplet radius of 10 μ	2.5%/min in droplets	Van Den Heuvel and Mason *(21)*
Atmospheric study of polluted areas in Japan	—	11.7%/min	Shirai et al. *(25)*
Atmospheric study of Canadian smelting area	150–4200 $\mu g/m^3$ SO_2	0.035%/min	Katz *(26)*
Study of SO_2 oxidation in plume of coal-burning power plant	Found moisture level in plume important; SO_2 6 g/m^3	0.1%/min at 70% RH 0.5%/min at 100% RH	Gartrell et al. *(27)*
Atmospheric study of Rouen (industrial city) in winter	68–242 $\mu g/m^3$ SO_2	6–25%/hr	Benarie et al. *(28)*

represent atmospheric sulfates. Another problem, perhaps related is the report that the concentration of sulfates in air depends upon the sampling volume. Much work needs to be done to solve these problems and to analyze critically and standardize the various sulfate measurements. Sampling and analysis of atmospheric sulfuric acid can most optimistically be described as in the development stage and further effort is required. Establishment of techniques to characterize the chemical composition of atmospheric sulfates is an essential step toward the understanding of health effects. It should be noted that as much as 80% of particulate sulfates collected in urban areas are in a size range small enough to be inhaled into the alveolus of the lung *(32, 33)*. In addition, further information is required concerning the relationship of ambient levels of sulfur dioxide to ambient levels of suspended sulfates. Available information suggests that this is not a simple linear function *(29)*.

In summary, evaluation of the atmospheric chemistry of sulfur oxides produces the following conclusions: (1) the rate of oxidation of sulfur dioxide to sulfuric acid and its conversion to suspended sulfates is greatly accelerated in polluted air; (2) the atmospheric chemistry of these reactions is highly complex and incompletely understood, and present information is mainly qualitative rather than quantitative; (3) in order to understand fully the relationship of ambient sulfur oxide levels to health effects, much more work is required to identify and characterize the various forms of sulfate present in the atmosphere, the processes by which they are produced, and their relationship to point or area sources of sulfur dioxide.

Background Review: Toxicology

The demonstration of a cause-and-effect relationship between exposure to sulfur oxides and adverse health consequences is based in part on experiments in which animals and human subjects are exposed to controlled atmospheres in the laboratory. Such studies permit the assessment of physiological changes caused by exposures of known duration to pollutants of known concentration. The controlled atmospheres used in laboratory experiments do not simulate urban air pollution accurately, and the detection of physiological responses does not necessarily indicate an adverse health effect. Nevertheless, studies in exposure chambers give clues to the kinds of effect to be expected from exposure to atmospheres containing the pollutants which have been studied in the laboratory.

SO_2 in Particle Free Air

Animal Studies: SO_2 is a respiratory irritant with high solubility in the aqueous lining membranes of the respiratory passages. Because of its high solubility, SO_2 is largely absorbed in the nose and upper respiratory passages and very little reaches the lungs. To produce death or pathological changes in the lungs of experimental animals, very high concentrations are needed. SO_2 inhalation produces bronchial narrowing as indicated by increased airflow resistance. This effect occurs in a matter of minutes and is readily reversible, suggesting that it results from an increase in bronchial smooth muscle tone *(35)*. The effect has been observed in guinea pigs, dogs, and cats as well as in human subjects. Exposure of guinea pigs to SO_2 levels up to 5.72 ppm (17,000 $\mu g/m^3$) for 12 months produced no identifiable effects apart from slight changes in the liver *(36)*. Monkeys exposed continuously for 78 weeks to SO_2 levels of 0.14−1.28 ppm (400−3800 $\mu g/m^3$) showed no significant pathological changes *(37)*. After exposure of rats to 1 ppm SO_2 (3,000 $\mu g/m^3$) for 170 hr, a significant depression of lung clearance of inert particles was demonstrated *(38)*. The effect of SO_2 was studied in Syrian hamsters who had been made emphysematous by exposure to an aerosol of 3% papain. The animals were exposed to high concentrations of SO_2 (650 ppm; 1,950,000 $\mu g/m^3$) for 4 hr per day, 5 days per week, for a total of 19−74 exposures. Only mild bronchitis and minor changes in the mechanical properties of the lungs were observed *(39)*. While conceptually attractive, this study is difficult to interpret because of the exceptional tolerance of the Syrian hamster to SO_2.

Human Studies: Although there is considerable variation in response in different people and in the same person at different times, most people show changes in respiratory flow resistance at SO_2 concentrations of 5 ppm (15,000 $\mu g/m^3$) and above. Especially sensitive people react to concentrations in the 1–2 ppm range (3000–6000 $\mu g/m^3$) *(35, 40–42)*. After 120 hr of exposure to 3 ppm (9000 $\mu g/m^3$) SO_2, increased small airway resistance and significant but minimal decrease in the dynamic compliance of the lung was noted in normal human subjects. The effect disappeared within 48 hr after cessation of exposure *(43)*. Four week-long exposures of subjects with demonstrable peripheral airway disease to SO_2 levels of 0.0, 0.3, 1.0, and 3.0 ppm (0, 900, 3000, and 9000 $\mu g/m^3$) produced no pattern relating to SO_2 dose *(44)*. The study was difficult to carry out, and the data showed wide variance.

In recent studies of normal human subjects, nasal mucus flow was measured by external detection of the movement of a very small radioactive particle placed on the mucosal surface inside the nose *(42)*. Mucus flow about half way from the tip of the nose to the nasopharynx decreased on the average to 80% of control values after 1–3 hr exposure to 1 ppm (3,000 $\mu g/m^3$) SO_2 in particle free air and decreased further to 54% of the control value after 4–6 hr exposure. Gas samples taken from the nasopharynx after passage through the nose contained less than 1% of the SO_2 which entered the nose, indicating that more than 99% had been absorbed in the nose. This confirmed earlier studies in animals and in healthy people. Mucus flow was slowest in the anterior part of the nose where the concentration of SO_2 was the highest, and was fastest in the posterior part of the nose where little SO_2 remained in the air. On forced expiration through the mouth, the air flow rate was reduced to an increasing degree with increasing concentrations of inspired SO_2 and with increased duration of exposure. In view of the very low concentrations of SO_2 reaching the bronchi, the reduced maximum expiratory air flow is thought to have resulted primarily from a nasobronchial reflex causing bronchoconstriction.

The absorption of SO_2 by the nose minimizes the exposure of the lower airways and lungs to SO_2, but interferes with mucus flow in the nose. This impairment of mucociliary clearance would be expected to reduce the capability of the respiratory tract for dealing with airborne particles, whether infectious, toxic, or inert, but direct evidence to this effect in humans is not yet available. When the nose is by-passed by breathing through the mouth, the trachea and bronchi are exposed to much higher concentrations of SO_2 than with nose breathing and adverse effects are greater.

SO_2 and Particulate Sulfur, Including Sulfuric Acid and Sulfate Salts

Mixtures of SO_2 and aerosols often have a greater irritant effect than would be expected from the two components acting independently *(35, 40, 41, 45)*. This more than additive effect, called synergism, is due to the transformation of SO_2 into a variety of products, including sulfuric acid and sulfate salts, which are more highly irritant than SO_2 itself.

Aerosols of soluble salts form droplets in humid air, and SO_2 dissolves in the droplets. This can occur in the atmosphere when the relative humidity is high or in the respiratory passages where the air rapidly becomes saturated with water vapor. The tiny droplets carry the SO_2 more deeply into the respiratory airways than it would otherwise go and also provide an aqueous medium in which chemical transformations can take place. Aerosols in the submicron size range penetrate more deeply and potentiate the irritant effect of SO_2 to a greater extent than larger particles. The irritant effect of a given droplet is increased by transformation of dissolved SO_2 into more highly irritant substances such as sulfuric acid and metallic sulfates.

Animal Studies: The synergism between SO_2 and particulates has been demonstrated by studies using mortality and lung pathology as criteria as well as in studies using changes in airway resistance and in clearance of inert particles and viable bacteria from the lungs *(35, 40, 41, 45)*. The presence of particulates capable of oxidizing SO_2 to sulfuric acid caused a 3- to 4-fold potentiation of the irritant response in guinea pigs *(41)*. Soluble salts of ferrous iron, manganese and vanadium were shown to pro-

duce this potentiation even at SO_2 concentrations as low as 0.16 ppm (480 $\mu g/m^3$). This concentration is occasionally seen in urban atmospheres. The metallic salts which acted as catalysts in these experiments were used at concentrations of 0.8 to 1 mg/m^3, which is higher than has been reported in urban air. Insoluble aerosols, such as carbon, iron oxide fume, triphenyl phosphate, or fly ash did not cause a potentiation of the irritant action of SO_2.

Recent experiments using guinea pigs have demonstrated that the synergism between SO_2 and aerosols of common salt, sodium chloride, are critically dependent on relative humidity *(46)*. At relative humidities above 70% the salt particles become droplets in which chemical reactions with SO_2 can occur before the aerosol is inhaled. Under these conditions synergism occurs as indicated by increase in airway resistance. Below 70% relative humidity the salt particles remain in the air as nonreactive crystals, and no synergistic effect upon airway resistance is seen. Since the humidity of air in the respiratory passages is always high, one can infer that the formation of droplets in the outside air, before entry into the airways, is of critical importance in relation to irritant effects.

Experiments in which animals were exposed to SO_2 alone or in combination with various insoluble dusts did not demonstrate increased susceptibility to bacterial infection *(47)*.

Mutagenic changes in viruses and bacteria have been attributed to the bisulfite ion which is one of the reaction products of SO_2 in water *(48–50)*.

Human Studies: Studies in which people have been exposed to combinations of SO_2 and sodium chloride aerosol have not consistently shown the synergistic effect seen in guinea pigs *(35, 41)*. Human exposures to mixtures of SO_2 and metallic aerosols which produce irritant sulfates have not been reported, and there are no human exposure data concerning combined effects of sulfur oxides and other commonly occurring pollutants such as nitrogen oxides, ozone, or hydrocarbons.

Summary

SO_2 and products into which it may be converted in the air are irritating to the lining membranes of the respiratory tract.

The irritant effect causes reflex bronchoconstriction, slowing of mucus flow, depression of clearance of inert particles from the lung, and, in regions of high concentration, narrowing of airways from inflammatory swelling of membranes.

Synergism between SO_2 and soluble aerosols has been demonstrated in animals. The necessary experiments have not yet been performed under controlled conditions using human subjects.

Increased susceptibility to infection has been looked for, but not found, in animal experiments, and has not been looked for in people under controlled conditions.

Bisulfite, one of the reaction products of SO_2 in droplets, has been shown to have mutagenic effects on viruses and bacteria. The significance of this finding to human health, if any, cannot yet be evaluated.

The physiological responses found under controlled conditions give useful insights into mechanisms of action, but cannot be translated directly into adverse effects of exposures to contaminated urban air.

Background Review: Epidemiology

Acute Episodes

The acute episodes of high pollution which have occurred in the Meuse Valley, Belgium, Donora, London, New York City, Osaka and elsewhere *(51–56)* provide the clearest evidence of an effect of air pollution on health. The increased mortality and morbidity which occurred in these episodes of pollution probably affected predominantly those who already were suffering from some chronic illness, particularly of the heart or lungs. These excess deaths occurred in age groups above 45 years in both London *(57)* and New York *(58)*; in addition, the individuals who were affected at Donora *(59)* were primarily those who had preexisting chronic disease. Gore and Shaddick *(60)* concluded from their analysis of episodes during the winters of 1954–1955 and 1955–1956 that a critical level of four times the customary winter average of air pollution in London would result in excess deaths. Subsequently, Burgess and Shaddick *(61)* suggested

that this would happen when smoke concentrations rose above $\mu g/m^3$ 2000 and SO_2 above 0.4 ppm (1144 $\mu g/m^3$).

Variation in Mortality, Morbidity, and Lung Function Over Time

Since 1958 in London, daily measurements of smoke and SO_2 have been related to daily deaths and illnesses *(62)*. Mortality and morbidity for all causes and for certain respiratory diseases were fairly highly correlated with both smoke and SO_2 levels until 1962; since 1962–1963, however, there has been little evidence of any effect of pollution on mortality or morbidity. It seems reasonable to attribute this change to the great reduction in smoke pollution which has been achieved in London during the last 15 years. During this time, smoke has declined from an average annual level of about 300 $\mu g/m^3$ to less than 50 $\mu g/m^3$ and SO_2 from a slightly higher concentration to about 200 $\mu g/m^3$. Lawther, reviewing these data for the period November 1958 to February 1959 concluded that increased mortality would result when daily smoke rose above 750 $\mu g/m^3$ and SO_2 above 0.25 ppm (710 $\mu g/m^3$).

Fletcher and his colleagues *(63)* made regular observations on 1000 men aged 30–59 living in North London from 1961 to 1966. The incidence of respiratory illnesses was found to be related to both smoke and SO_2 levels. Illness attack rates increased when weekly smoke concentrations exceeded 400 $\mu g/m^3$ and SO_2 exceeded 0.16 ppm (458 $\mu g/m^3$). An increase in symptoms and decrease in ventilatory lung function appeared to be associated with daily rises in smoke concentrations above 300 $\mu g/m^3$ and SO_2 concentrations above 0.21 ppm (600 $\mu g/m^3$). During the period of observation, there was a decline in the volume of morning sputum produced by the men under observation. This could have been due to the concurrent reduction in air pollution but it might also have been due to a reduction in the tar content of cigarettes, which also occurred at the same time.

In an attempt to study a more susceptible group of people, Lawther and his colleagues *(64–69)* have been making observations on bronchitic patients. Each patient keeps a daily record of changes in his health in a pocket diary, and records whether his chest is better, worse, or the same as usual. A close correlation between the concentration of smoke and SO_2 and the clinical condition of the patients during the winter months was noted. In the earlier years (1959–1960), the correlations were higher than 5 yr later (1964–1965), when the concentration of smoke in London had been considerably reduced. The patients appeared to be most sensitive to changes in pollution early in the winter. The minimum pollution level which leads to a significant response was about 500 $\mu g/m^3$ SO_2 with about 250 $\mu g/m^3$ smoke. These authors considered that the effects they observed were more likely to be due to brief exposures to the maximum concentrations occurring during the day than to the 24-hour daily levels. Moreover, they noted that correlations between health status and pollutant levels were still demonstrable in 1967–1968 when the annual concentration of smoke was 68 $\mu g/m^3$ and of SO_2 204 $\mu g/m^3$.

Studies of bronchitic patients were carried out in Chicago by Burrows et al. *(70)*. The severity of symptoms was found to vary with temperature and SO_2 level. When season and daily temperature were held constant, however, only hydrocarbon levels showed an independent correlation with symptoms. The authors concluded that air contaminants did not appear to play a major role in the daily variation in the patients' symptoms. However, Carnow et al. *(71)* who also studied patients in Chicago, found that illness rates increased with increasing exposure to SO_2. The critical level at which this increase occurred appeared to be about 0.25–0.30 ppm SO_2 (710–858 $\mu g/m^3$). Particulates were not included in this analysis. They were probably high since in 1966–1967, the time the study was carried out, the average annual concentration of particulates in Chicago was 148 $\mu g/m^3$.

Geographical Comparisons

One way in which the effects of pollution may be studied is to compare people who live in areas which differ in air pollution. Comparisons may be international, national, or local. They may be of persons living in urban and rural areas, in cities which differ in their pollution, or in different areas of a single large city.

International Differences

The large differences in bronchitis mortality among different countries has sometimes been

attributed to differences in pollution among them. But it has become increasingly clear that diagnostic practices differ in different countries, and that variations in death certification account for much of the variation. However, when these are allowed for, there are still differences in mortality and morbidity between different countries. Some of these could be due to differences in air pollution. Some of the difficulties inherent in carrying out international comparisons are indicated by the studies conducted by Ferris and Anderson *(72, 73)*. The authors compared respiratory disease and lung function in representative samples of the inhabitants of two towns which differed in their degree of air pollution. In 1961 they studied a 1:10 sample of adults living in Berlin, New Hampshire. Two years later, they carried out a comparable study of a 1:7 sample of the inhabitants aged 25–74 of Chilliwack, British Columbia. In each survey, methods were comparable and the observers the same. One major cause of differences between surveys was therefore largely eliminated.

Information about respiratory symptoms and smoking habits was obtained by using a prototype of the British Medical Research Council's respiratory symptoms questionnaire. The forced expiratory volume (FEV) and peak expiratory flow rates (PEFR) were used to assess ventilatory lung function. On the basis of the age/specific prevalence of symptoms in both surveys, expected rates for non-smokers were calculated. From the multiple regression equations on age and height for the FEV and PEFR for Berlin, expected lung function values were calculated for Chilliwack. There was little difference in respiratory disease prevalence of male non-smokers from that expected, but in women the prevalence was slightly below that expected. Lung function values were also consistently slightly higher than expected in both men and women in Chilliwack for all smoking categories. These differences are in the direction one would expect if pollution were exerting an effect. But, as the authors point out, they could still be due to ethnic differences between the two populations.

A further international comparison was made between the results from the general practitioners survey in Great Britain and that in Berlin, New Hampshire *(74, 75)*. In both instances the same questionnaire was used. In the British survey a panel of physicians was used whereas two other physicians surveyed the Berlin, New Hampshire population. No cross testing of the two groups of observers was done; but one of the observers in Berlin has worked with British workers using similar questionnaires and there have not been marked differences between the observers. A comparison of the results shows that Berlin, New Hampshire, has lower levels of particulates and SO_2 than the concentrations of large cities of Britain. The subjects were then categorized as simple chronic bronchitis (phlegm production for three months out of the year for the past 2–3 yr or more) or a complex chronic bronchitis (simple chronic bronchitis, plus bouts of cough and phlegm lasting for three weeks each winter and for more than two winters), and shortness of breath (such that the subject could not keep up with persons of his own age on the level). Only those 45–64 years of age were compared. When the data were standardized for cigarette smoking, no relationship was seen between the simple syndrome and air pollution. The complex syndrome, on the other hand, did show an increase across the levels of pollution which was approximately a 2 to 3-fold rise. A comparison of the tests of pulmonary function cannot be made with certainty as only peak flows were measured in Britain and there was no cross calibration of the meters. In general, values in the United Kingdom were lower for the same age, sex, and smoking category.

In another study a similar comparison was made between Britain and the United States and a comparable occupational group *(76)*. This study showed that the pulmonary function of the men in the United States was better than that in the United Kingdom. Differences in height in the two populations could not account for all of the difference. No statement was made as to the temperature corrections. If these results were expressed at ATPS, then the temperature differences between the two countries might account for the residual difference. The authors, however, attributed the difference to the different levels of pollution in the two countries.

Urban/Rural Gradients of Respiratory Disease Mortality and Morbidity

A striking feature of the mortality statistics of certain countries is a pronounced gradient between urban and rural areas in death rates for chronic respiratory disease. This trend is pronounced in the United Kingdom for both men and women. There is a similar, though much less impressive, trend for men, but none for women in the United States *(77)*. These observations have stimulated a great deal of research *(78–81)*. The earliest studies used available data *(82–86)*. Mortality rates in different areas were related to levels of air pollution where these were available. Mortality from bronchitis was found to be correlated with indices of pollution, social circumstances, and density of population. In many of these studies, however, cigarette smoking habits were not adequately controlled for.

Comparisons of Uniform Occupational Groups

To get around the difficulty that differences in exposure to air pollution tend to be confounded with differences in social class, Fairbairn and Reid *(87)* studied postmen, a uniform occupation group, who receive the same pay wherever they work and, once established, tend to remain in the same area. They found that premature retirement and death from bronchitis and pneumonia were related to thick and presumably polluted fog, and were independent of domestic overcrowding or population density. Somewhat similar observations were made in British transport workers *(88)*.

In the United States, surveys of Bell Telephone employees were carried out by Holland et al. *(89)* and by Deane et al. *(90)*. The results have been compared with studies carried out in a comparable manner in London and smaller towns in England. Differences in symptom prevalence, morning sputum volume, and lung function were observed, which were in a direction which would have been expected if pollution had been playing a role. A recent study of telephone workers in Washington, D. C., Baltimore, Manhatten, and Westchester County, N.Y., failed to show any significant association between pollution at home and at work and respiratory symptoms and level of ventilatory lung function *(91)*.

Comparisons between Towns

Comparisons have sometimes been made between towns which differ in air pollution. Dohan and Taylor *(92)* and Dohan *(93)* related claims for insurance benefits in female employees of the Radio Corporation of America to levels of pollution in five cities. They found a high correlation between respiratory illnesses of seven days' duration and over and average levels of suspended particulate sulfates for the years 1955–1957. Age distribution, conditions of work, and social and climatic factors did not appear to account for the five fold variation in the incidence of these illnesses between the cities.

A comparison of respiratory disease and lung function in two towns in Pennsylvania with contrasting levels of air pollution was carried out by the United States Public Health Service *(94)*. Average dust fall in Seward, the more polluted town, was 3.2 times and SO_2 was 6.2 times that of New Florence. Age- and height-adjusted mean values of most lung function tests were remarkably similar for both sexes in each town. The only exception was that the average airways resistance and airways resistance times volume were higher in Seward. It was not possible to conclude from this study that the difference in pollution caused the difference in airway resistance because there were other differences between the two towns (for example, the proportion of miners in each) which could have been responsible, and cigarette smoking was not controlled for.

Differences within a Large City

Differences in mortality and morbidity often occur in different areas of a single large city. It is sometimes possible to correlate these with differences in air pollution. Such studies have been carried out in Buffalo, New York *(95, 96)*. Pollution in Buffalo was monitored from 1961–1963, and levels of particulates and sulfation were related to mortality for 1959–1961. Total mortality in men and women aged 50 years and over and respiratory disease mortality in men

aged 50–69 were both significantly correlated with suspended particulate concentrations. There was no significant relationship between mortality and sulfation in this study, but the levels of sulfation recorded were low.

One of the most detailed studies of air pollution was conducted by the United States Public Health Service in Nashville, Tennessee *(97–99)*. Pollution was monitored by a network of 123 stations. Mortality from 1949 to 1960 was correlated with pollution levels. Age/specific death rates for respiratory disease at ages 25–74 were directly related to SO_2 levels and cardiovascular mortality to soiling. Various indices of morbidity, such as the frequency of asthma attacks, were also related to pollutant levels. Unfortunately, in neither the Buffalo nor Nashville studies was attention directed to smoking habits or occupation.

Studies of Children

A number of studies has been carried out on children, who are particularly suitable because they tend not to smoke cigarettes and for the most part do not engage in dusty jobs. They may also be exceptionally sensitive to the effects of pollution.

In Japan, Toyama *(100)* and Watanabe *(56)* found that school children living in Kawasaki and Osaka, two polluted cities, had lower peak flow rates than children living in less polluted areas. One of the most interesting studies of children was carried out in Britain by Douglas and Waller *(101)*. In 1946, a study of health and development was initiated. All children born in a one-week period in March were followed to school-leaving age in 1961. Subsequently, the illness experience of the children was related to the areas in which they had lived, and so to the probable levels of pollution experienced through life. The results showed that lower respiratory infections were consistently related to pollution but that upper respiratory infections were not. Both the frequency and severity of such infections increased with the amount of pollution. The lowest levels of smoke and SO_2 were 70 and 90 $\mu g/m^3$, respectively. Higher illness rates were added in all higher pollution classes.

Lunn et al. *(102)* studied the prevalence of respiratory illnesses in school children aged 5 years and 10 to 11 years living in four areas of Sheffield with differing air pollution. They found that both upper and lower respiratory infections increased with increasing pollution. The prevalence of symptoms was higher at annual means of smoke and SO_2 of about 200 $\mu g/m^3$ compared with about 100 $\mu g/m^3$. FEV and forced volume capacity (FVC) were lower in the most polluted area. A 4-yr follow-up *(103)* showed that most of the differences between the groups had disappeared with the reduction of smoke which had been achieved in Sheffield.

More recently, Holland et al. *(104)* studied some 10,000 school children in four areas of Kent. Peak expiratory flow was found to be related to area of residence, social class, family size, and a past history of pneumonia, bronchitis, or asthma. These four factors appeared to act independently and the effects were additive. The findings suggested that environment early in life can produce adverse changes which may persist and contribute to the development of chronic respiratory disease.

Ferris et al. *(105)* did a follow-up study in 1967 in the Berlin, New Hampshire population that had been studied in 1961. The levels of both sulfation rate and total suspended particulates had fallen by about 30–40%. After age standardizing within the various cigarette smoking categories, men and women tended to have lower frequencies of respiratory symptoms and less of a fall in pulmonary function than would have been expected by age. Levels of air pollution were 731 (±241) μg SO_3/100 cm^2/day in 1961 and 469 (±111) μg SO_3/100 cm^2/day in 1967; total suspended particulates were 180 ± 71 $\mu g/m^3$ in 1961 and 132 ± 83 $\mu g/m^3$ in 1967. Changes in smoking habits or use of filter-tipped cigarettes could not explain this difference. These results were interpreted as being confirmatory of those seen in the Berlin-Chilliwack comparison.

More recently, Cohen et al. *(106)* using a diary technique, looked at the effects of climate and air pollution on asthmatics. The sample was small. They found that temperature had more effect than air pollution and that all pollutants were associated with asthmatic attacks. There also seemed to be an interaction between temperature and pollution levels such that the effect

of the pollutants was greater at temperatures above 50°F than at temperatures below 30°F when the asthma attack rate was greatest.

A number of other studies have looked at these aspects and have concluded that there may well be such an interaction and that the effects of climate should be taken into account.

Lambert and Reid *(107)* carried out a postal survey of respiratory symptoms in a representative sample of men and women living in England, Wales, and Scotland. Of 18,379 men and women believed to be aged 35 or over in the households sampled, questionnaires were returned from 12,236. Of these, 2261 were outside the required age range of 35–69, 1155 refused, and 3614 did not reply. The 9975 questionnaires completed, thought to represent 74% of those aged 35–69 and able to respond, were analyzed. An increasing prevalence of persistent cough and phlegm and of chronic bronchitis (persistent cough and phlegm, breathlessness on walking, and a period of increased cough and phlegm lasting 3 weeks or more in the past 3 yr) with increasing age and with increasing cigarette consumption was confirmed. There was an excess in male nonsmokers as well as in smokers. Urban/rural gradients were not explained by smoking differences alone. The prevalence of symptoms increased with increasing air pollution independently of cigarette consumption. Local pollution appeared to have little effect on nonsmokers, but in smokers, high levels of pollution were associated with more frequent respiratory symptoms. Prevalence of symptoms increased progressively from the lowest (less than 100 $\mu g/m^3$ smoke and SO_2 on the average per year) to the highest (≥ 200 $\mu g/m^3$). This study, then, indicates that pollution had a clear effect on respiratory symptoms after allowing for age and cigarette smoking. There was also an interaction between smoking and pollution.

Recent Studies

During the past few years, as part of its Community Health and Environmental Surveillance System (CHESS), the Environmental Protection Agency has conducted a number of studies of the effects of air pollution on respiratory disease. Several of these have recently been published *(108–110)*. Levels of SO_2 and particulates, including suspended sulfates and nitrates, have been related to acute respiratory illnesses and chronic respiratory symptoms occurring in members of familes living in areas which differ in respect to pollution in four general communities. The communities were the Salt Lake basin area, Utah, five Rocky Mountain areas in Idaho and Montana, New York City and Chicago. Families were recruited through elementary or nursery schools. In the Utah and Rocky Mountain area, monthly averages of SO_2, sulfates and suspended particulates were derived from emissions estimates and dispersion models. Measurements were available only for 1971. In New York, total suspended particulates were collected daily by high volume sampler and analyzed for nitrate, sulfate, and organic fraction. SO_2 was measured three times a week by the modified West Gaeke method. In Chicago, particulates were measured three times a week and SO_2 once a week at an air monitoring station within 1.5 mile of the family's home. Health and demographic information on illnesses and respiratory symptoms was collected by self-administered questionnaires supplemented by telephone interviews. The questionnaires were completed for the family members by the mother or guardian. In each community the prevalence of chronic bronchitis (persistent cough and sputum for 3 months of the year either alone or with breathlessness when walking at an ordinary pace on the level) and the occurrence of various upper and lower respiratory tract infections in high and low pollution areas were compared. Higher rates were found in the higher pollution areas. A major aim of the studies was to define levels of pollution which resulted in an effect on health. The validity of self-reporting to accomplish this end is seriously open to question. Reporting is likely to reflect attitudes to present and past pollution and only limited checks of parental diagnoses with physicians records were made. One curious feature of the combined results of these studies in relation to chronic respiratory disease is that while in each community after allowance was made for smoking, the prevalence of chronic bronchitis was higher in the high than in the low pollution area, there were no corresponding differences between the communities. Chronic bronchitis was in fact lower in fathers and mothers in New York City

than in Utah despite the fact that pollution was much higher in New York City.

In a series of studies carried out in Cincinnati, Chattanooga, and New York City *(108)*, the forced expiratory volume of elementary school children was related to pollution. The FEV was found to be consistently lower in children 5–13 yr old exposed to higher concentrations of particulates and SO_2. In Cincinnati, the performance of children in polluted neighborhoods improved during the seasons of low pollution but not to the level of their counterparts in the low exposure neighborhoods. The results are presented graphically and in insufficient detail for the bases for these conclusions to be checked. Nor is sufficient evidence presented that differences between neighborhoods was not due to differences in the performance of the lung function test. We are not told who performed the test in each area. If a number of observers were involved, no measurements of observer variation were made. All in all, it is not at all clear that the differences in lung function between neighborhoods which were shown in these studies can be attributed to differences in air pollution between them.

In a recent study of bronchitic patients in London, Emerson *(111)* made several spirometric measurements at weekly intervals over periods of 12 to 82 weeks. The changes observed were correlated with daily atmosphere and air pollution measurements. Significant correlations of $FEV_{1.0}$ with temperature in six patients, humidity in four and with barometric pressure in three were found. In only one was there a correlation with SO_2 levels and in none with smoke. The conclusion drawn was that at the concentrations of these pollutants now existing in London SO_2 and smoke have little effect on ventilatory lung function of patients with chronic airways disease. The concentrations during this study were: smoke, mean annual 41 and maximum daily 241 $\mu g/m^3$; SO_2, mean annual 187 and maximum daily 730 $\mu g/m^3$. This study might perhaps suggest that, provided smoke concentrations are low enough, somewhat higher levels of SO_2 than are now permitted by the primary standards might be permitted.

On the other hand, a recent study of mortality in the United States *(112)* from 1962 to 1966 showed that while the main predictors of mortality were: annual cycle, day of the week, Christmas holidays, influenza epidemics and days or spells of extreme temperatures, pollution as measured by coefficient of haze units (COHS) and SO_2 contributed to a small but significant extent. In New York City, mortality was 1.5% less than expected when SO_2 was under 30 $\mu g/m^3$ and 2% greater when it was above 500 $\mu g/m^3$. This in fact suggests that there might be no threshold and that the lower the concentration of SO_2, the lower will be the possibility of adverse health effects.

Dose/Response Relationships, Old Results

We can form some idea of the levels of smoke and SO_2 which may cause effects (Table 5) *(113)*. It is important to realize that these two pollutants may not be the most important, but instead only indices of others that are more important. In London, mortality has clearly resulted when 24 hr concentrations of smoke have risen to 1000–2000 $\mu g/m^3$ and to concentrations of SO_2 of 750 $\mu g/m^3$. These sorts of levels may occur with average annual concentrations of smoke of 300–400 $\mu g/m^3$ and of SO_2 of 250–300 $\mu g/m^3$. No one can doubt that these concentrations are far too high and should not be allowed.

In London, 24 hr values of about 500 $\mu g/m^3$ smoke and 400 $\mu g/m^3$ SO_2 have led to exacerbations among bronchitis patients. Now that the average concentrations of smoke and SO_2 in London are about 40 and 170 $\mu g/m^3$, respectively, it will be interesting to see if there is still any response among these susceptible patients to the highest levels which occur in the winter.

In the whole of Britain, correlations which appear to be linear can be shown for bronchitis sickness absence when winter smoke and SO_2 rise above 100–700 $\mu g/m^3$. Similarly respiratory symptom prevalence and respiratory infections in children rise with increasing pollution levels above 100 microg/cu.m. In New York City, 24-hr averages of 6 coefficient of haze units (COHS) and 2000 $\mu g/m^3$ have resulted in mortality and 3 COHS and 700 $\mu g/m^3$ in morbidity.

In Buffalo, there was a steady increase in respiratory mortality from the lowest to the

Table 5. Summary of dose–response relationships for effects of particles and SO_2 and health.

Averaging time for pollution measurements	Approximate levels of pollution: Place	Particles, $\mu g/m^3$	SO_2, $\mu g/m^3$	Effect
24 hr	London	2000	1144	Mortality
24 hr	London	750	700	Mortality
24 hr	London	300	600	Deterioration of patients
Weekly mean	London	200	400	Prevalence or incidence of respiratory illnesses
24 hr	New York	6[b]	1500	Mortality
Winter mean	Britain	100–200	100–200	Incapacity for work from bronchitis
Annual	Britain	70	90	Lower respiratory infections in children
	Britain	100	100	Upper and lower respiratory infections in children
	Britain	100	100	Brochities prevalence
	Britain	100	100	Prevalence of symptoms
	Buffalo	100	300[c]	Respiratory mortality
	Berlin, N.H.	180	731[c]	Increased respiratory symptoms Decreased pulmonary function

[a]"Old" results, leading to original standards.

[b]In coefficient of base units (COHS).

[c]As $\mu g\ SO_3/100\ cm^2/day$.

highest pollutant levels. The lowest particulates levels were under 80 $\mu g/m^3$ and sulfation was less than under 0.30 mg $SO_3/cm^2/day$.

On the basis of these figures, average annual values of something under 100 $\mu g/m^3$ for particulates and SO_2 and something under 300 and 600 $\mu g/m^3$ for 24 hr would seem to be desirable. The primary standards reflected this. What conclusions can be drawn from more recent studies about their adequacy?

New Results

The CHESS studies have provided the largest body of data which might perhaps suggest that the primary standards may be too high and should be lowered. We believe that the methods used, the sampling, the internal inconsistency of the findings and other questions render the validity of the findings too uncertain to justify these conclusions. Nor do we think that these studies provide a sound basis for a standard for suspended sulfates. More research is needed on this topic. British experience might suggest that the major effort should be put on reducing particulates. We are in some difficulty, however, in trying to generalize from British experience since the type of pollution and methods of assessing it are different in Britain and in the United States.

With the implementation and enforcement of the primary Federal air pollution standards, we have reached a stage where pollution is unlikely to cause much adverse effect on health. Further reduction of the standard might protect a few sick people from being made worse by air pollution, but of this there is considerable doubt (Table 6). Such reduction would be disproportionately costly when related to the likely benefits which could be expected. Such cost should only be accepted on the basis of convincing evidence that standards are now too high. The only satisfactory evidence that would justify this conclusion would come from well designed experiments. It would be justifiable to select some comparable cities; monitor pollution and inhabitants carefully, employing objective tests wherever possible; reduce particulates and SO_2 in one city, particulates in another, possibly enforce particulates at standard but allow SO_2 to rise modestly in a third and maintain standards in a fourth (Figure 4). The costs and benefits of the various procedures might then be adequately measured. We doubt if the information we now need can be obtained in any other way.

Table 6
Expected Health Effects of Air Pollution On Selected Population.

Effect	Pollutant	
Excess mortality and hospital admissions (24 hr mean)	500	500
Worsening of patients with pulmonary disease (24 hr mean)	250	500–250
Respiratory symptoms (annual arithmetic mean)	100	100
Visibility and/or annoyance (annual geometric mean)	80	80

World Health Organization (WHO) data.

Maintain* TSP Maintain SO_2	Maintain TSP Allow SO_2 to rise (say, to 100 $\mu g/m^3$)
Reduce TSP Maintain SO_2	Reduce TSP Reduce SO_2

FIGURE 4. Experimental design. Asterisk (*) refers to primary Federal standards.

Interim Report: Review of Health Effects of Sulfur Oxides in the Ambient Air

Preliminary Findings

Following review of the available data and presentations by experts from the United States and abroad, it seems that the current primary ambient air standards for sulfur oxides (SO_2) are likely to be reasonable and in the proper range. We are continuing our analysis of the data in this area and will present more specific conclusions in our final report.

Nature of the Scientific Problem

SO_2 is a gas whose concentration in the atmosphere is used as an index of the extent of air pollution. When studied alone, it acts as a relatively nontoxic gas. In the ambient air, it undergoes chemical reaction to much more toxic substances, namely suspended sulfate particles and sulfuric acid mist. Additional epidemiologic studies are needed to verify the health effects of these products. These studies will require the development of improved monitoring methods and the establishment of a complete data base for sulfates (particularly in the particulate fraction) in the air. SO_2 levels in the ambient air appear to be a reflection of air pollution levels since SO_2 is the major precursor of the more toxic sulfur reaction products.

Nature of Standards

A Primary Ambient Air Standard states the concentrations of a given substance which on the basis of the "best available scientific evidence" are likely to cause no adverse health effects to the general population in the United States. "Best available scientific evidence" is an important concept because it indicates that the standards will change as we gather more knowledge about health effects of individual pollutants. With scientific advances, this standard will approach a "no effects level" for each pollutant based on a natural law of chemical-biological interaction. As we approach this natural limit, our margin of scientific error decreases. The Clean Air Act requires that a safety factor be added to each air quality standard to approximate the scientific error and to insure that the American people are adequately protected from the health consequences of each agent. Thus, the Primary Standard is the scientist's best estimate of a natural law of chemical-biological interactions which defines the highest concentration of a pollutant that will cause no damage to health. It includes an estimate of scientific error in terms of a legal safety factor.

Policy Decisions and the Standard

In the long run we are convinced that this identification of the natural law relationship will establish concentrations of SO_2 and other pollutants which do not damage human health. SO_2

levels however must not be considered in a scientific vacuum. We are well aware that modern man lives in a society which exposes him to a surprising variety of interrelated risks. Once these laws are identified, the difficult choices between interrelated risks can be made on an objective, scientific basis. In extreme situations, one standard or another might be appropriately and knowingly exceeded so as to ameliorate a related situation and thus cause the least possible harm to human health.

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